Alan Ho, Mudassir Lodi, Max Mekhanikov

Functions Used

GeneNet(a0,a,b,n,m1,m2,m3,p1,p2,p3)
TimeSeries(F,x,pt,h,A,i)

Parameters

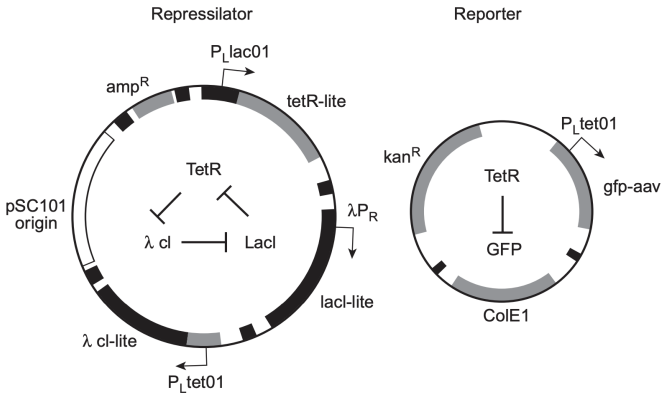
a0= rate of transcription of mRNA in the presence of a saturating concentration of repressor
a = the additional rate of transcription in absence of inhibitor
b = the ratio of the rate of decay of protein to mRNA
n = a “cooperativity” coefficient in the function describing the concentration dependence of repression

Biological Background

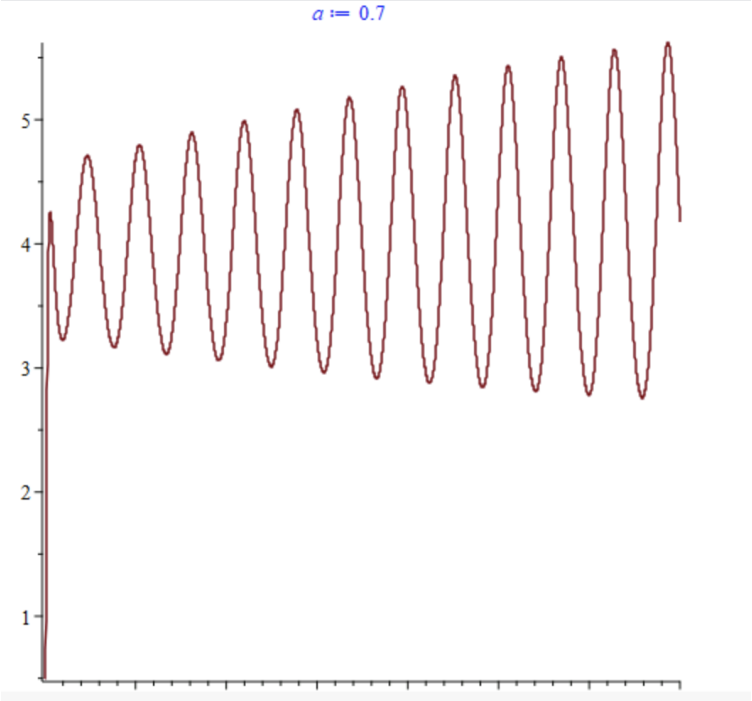
Gene expression is a highly regulated process that involves intricate chemical reaction networks in conjunction with activators, inhibitors, transcription factors and much more. The rates of DNA transcription and translation are independently controlled and are regulated by a multitude of simultaneous cellular factors. This abundantly complex and intricate process has posed insurmountable problems for researchers who have sought to quantitatively model these systems, despite the exponential increases in biotechnology and bioinformatic tools in recent years. In order to bypass these limitations, a new “synthetic biology” approach has been developed in which biological systems are engineered first and then compared to simple models (instead of designing models around experimental cellular data).

In this review we will be discussing a model proposed by Elowitz and Leibler (2000) in which they constructed a network to model an *E. Coli* bacterium with 3 inserted repressors. There is a circular system of repression in which one inhibits transcription of the next, which in turn inhibits transcription of another, and finally inhibits transcription of the first repressor. In this model, there are two possibilities of the long-term concentration of mRNA and protein.

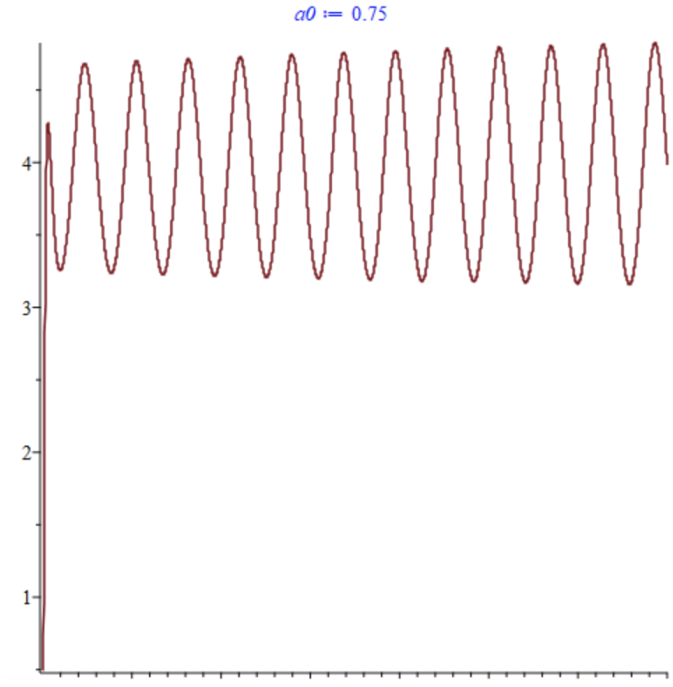
First, a predictable steady-state concentration is possible in the absence of inhibition. However, long-term oscillations are also possible whenever cross-inhibition is introduced. In this type of equilibrium, high concentrations of one protein will inhibit transcription of another protein, which will stimulate production of the last protein, which will round back to inhibit the first protein. In other words, the concentration of each repressor waxes and wanes as time progresses, creating oscillations.



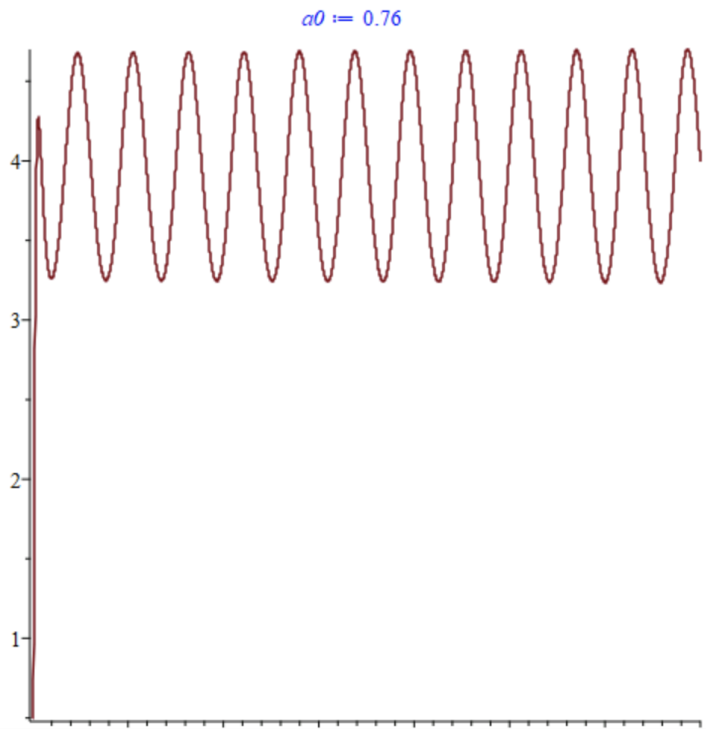
a0 parameter = rate of transcription of mRNA in the presence of a saturating concentration of repressor



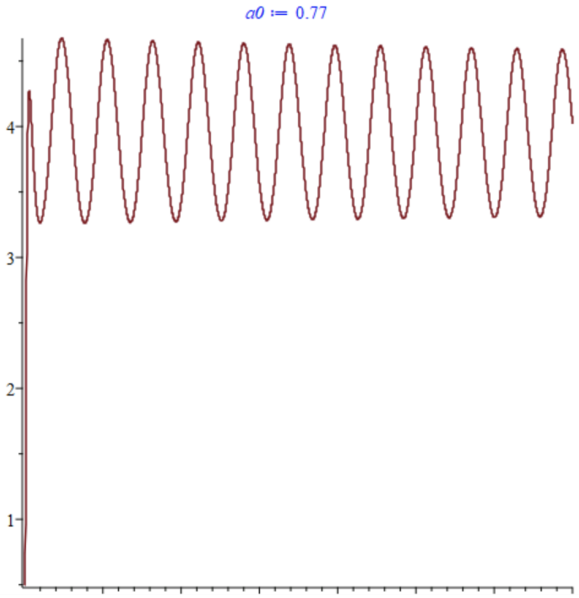
(a0,a,b,n) = (0.7, 50, 0.2, 2)



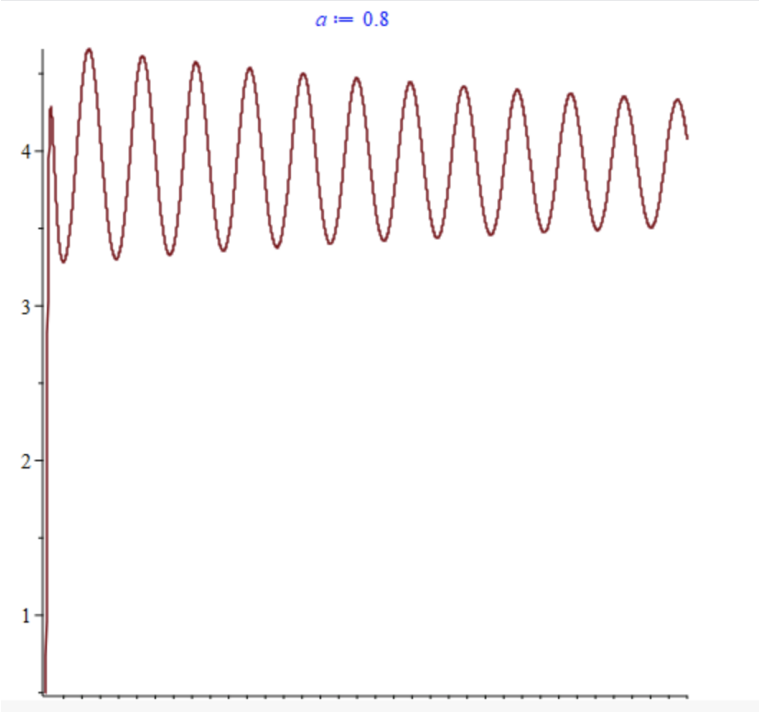
(a0,a,b,n) = (0.75, 50, 0.2, 2)



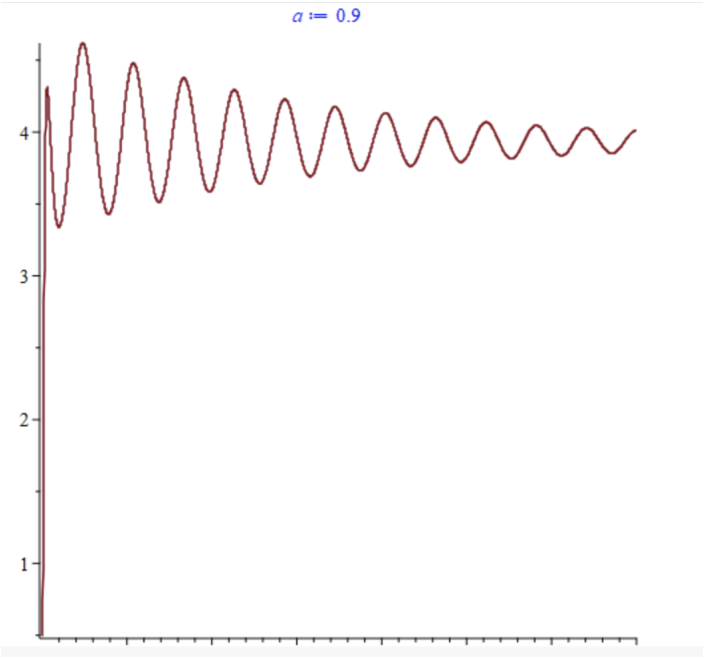
(a0,a,b,n) = (0.76, 50, 0.2, 2)



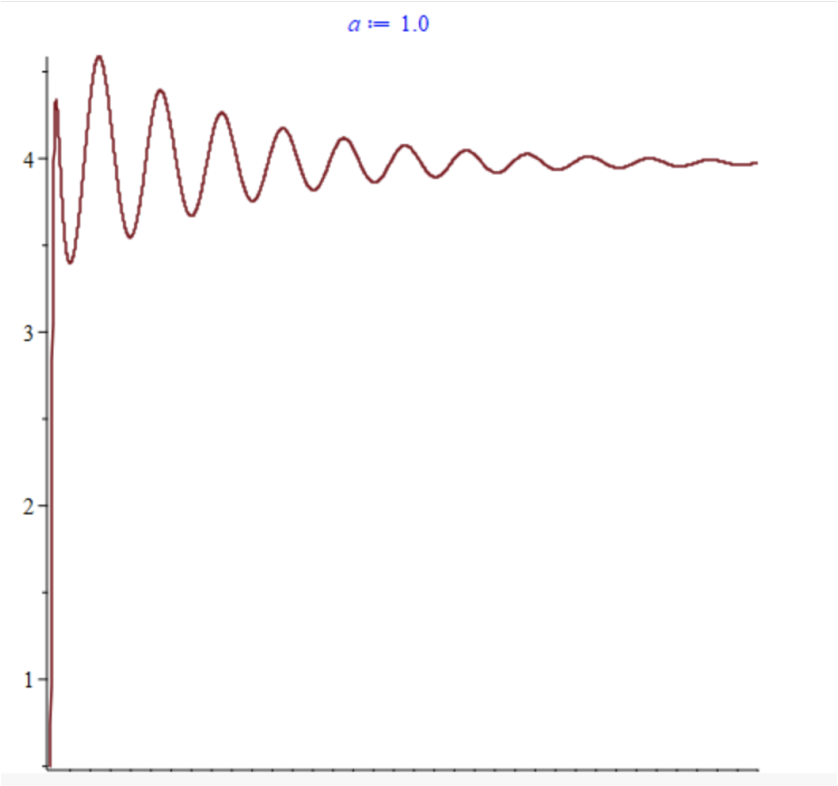
(a0,a,b,n) = (0.77, 50, 0.2, 2)



(a0,a,b,n) = (0.8, 50, 0.2, 2)



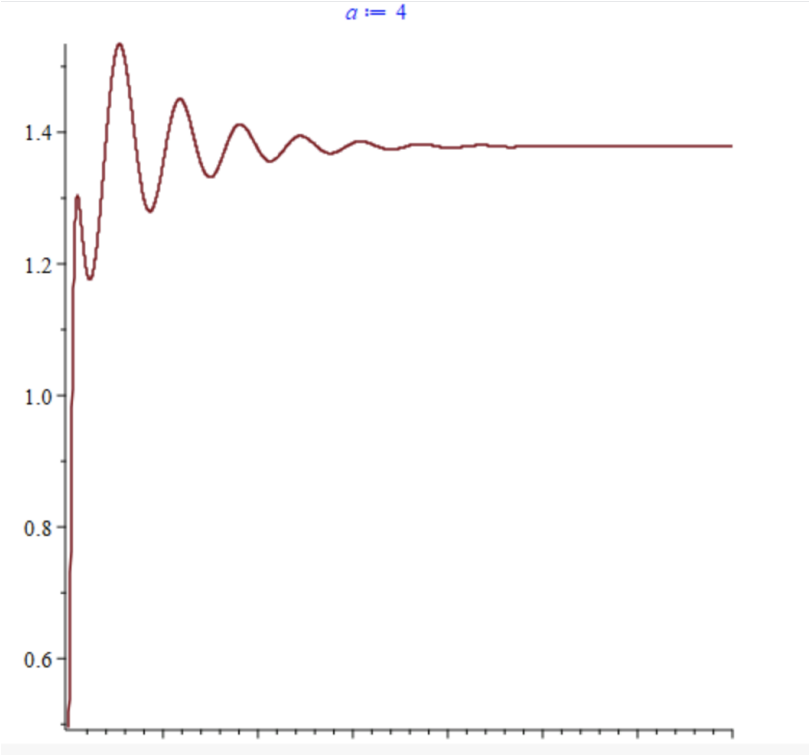
(a0,a,b,n) = (0.9, 50, 0.2, 2)



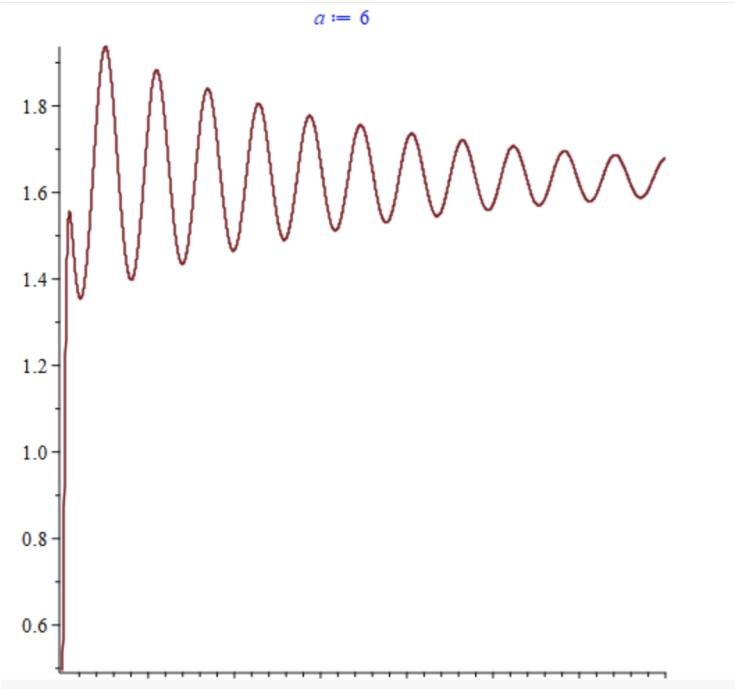
(a0,a,b,n) = (1.0, 50, 0.2, 2)

The long-term behavior of the system is initially periodic oscillations when a0 = 0. Incrementing a0 by 0.01, the long-term behavior changes when **a0 = 0.77.**

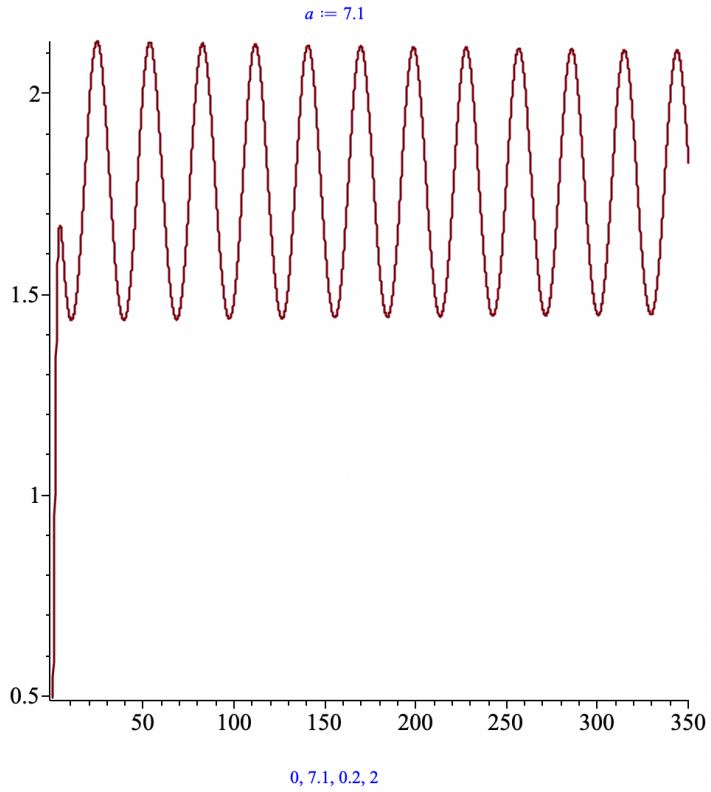
a = the additional rate of transcription in absence of inhibitor



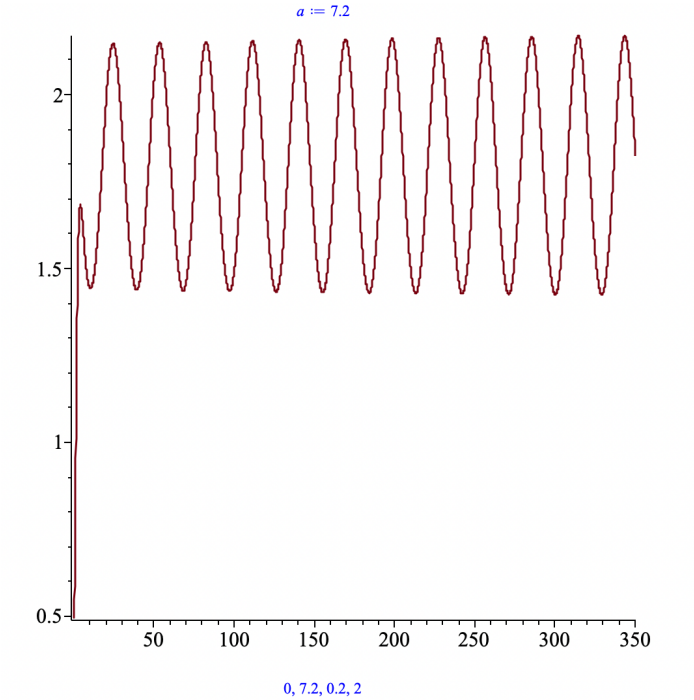
(a0,a,b,n) = (0, 4, 0.2, 2)



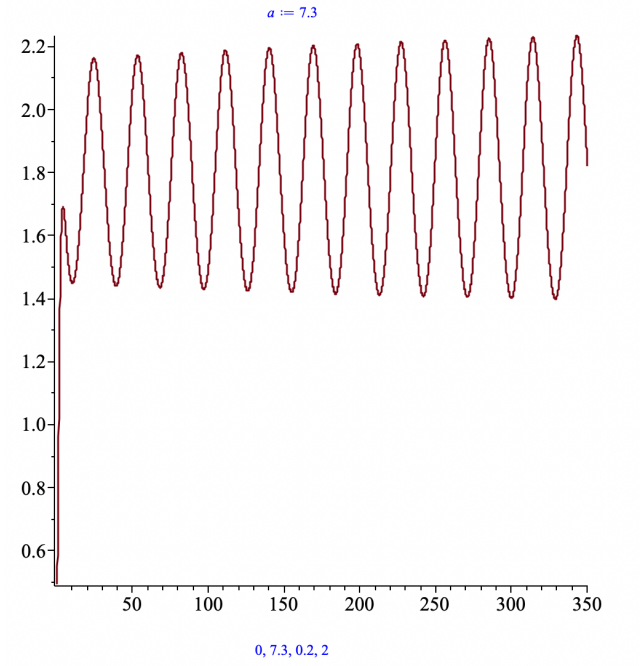
(a0,a,b,n) = (0, 6, 0.2, 2)



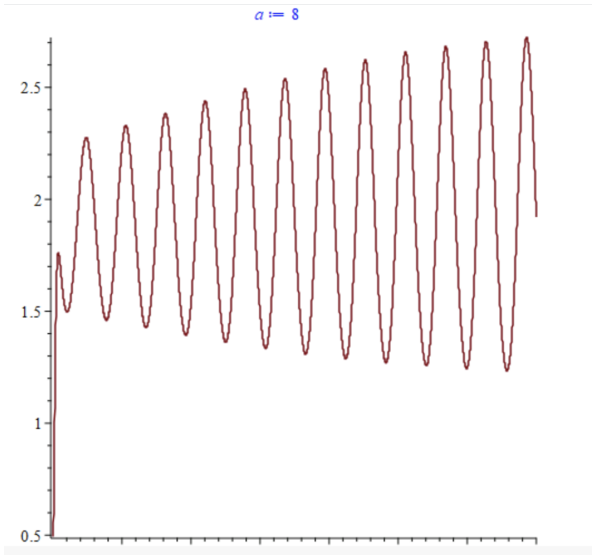
(a0,a,b,n) = (0, 7.1, 0.2, 2)



(a0,a,b,n) = (0, 7.2, 0.2, 2)



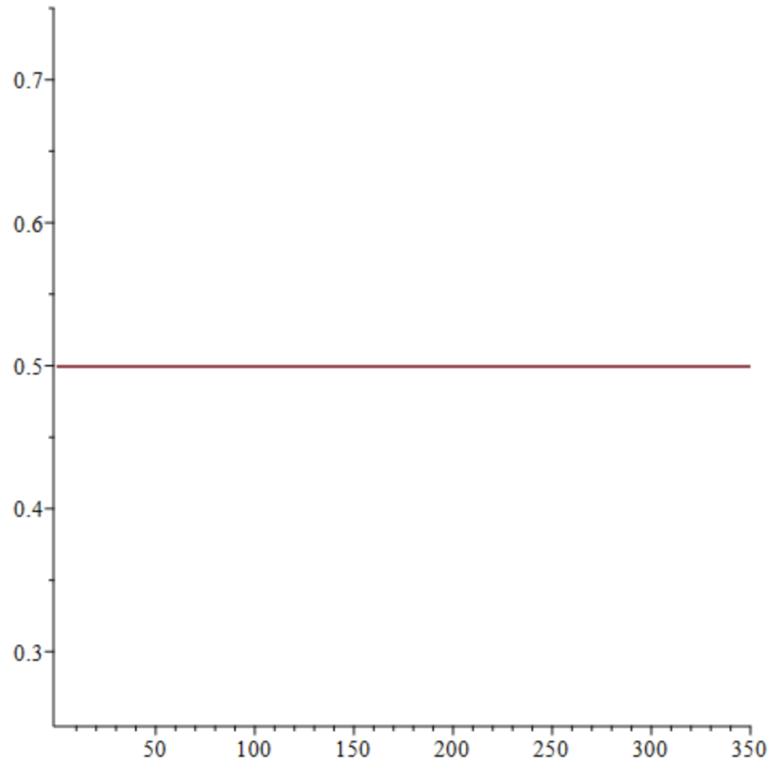
(a0,a,b,n) = (0, 7.3, 0.2, 2)



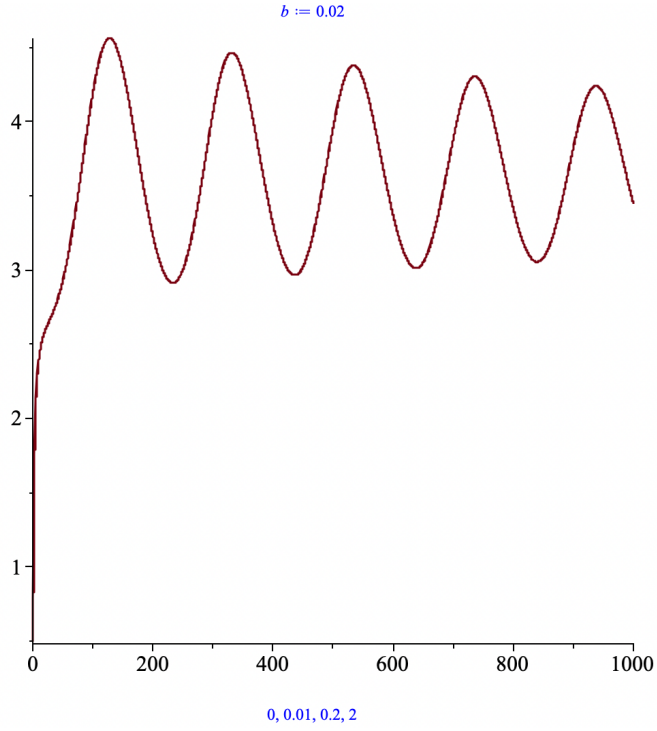
(a0,a,b,n) = (0, 8, 0.2, 2)

- Parameter “a” is defined as the difference between transcription rates in the absence of a repressor and in the presence of a repressor. Therefore, when “a” remains small, there are no solutions that oscillate and all solutions approach equilibrium. A larger “a” value indicates that oscillations are more likely to occur because repressors bind tightly and reduce transcription rates substantially.
- **The long-term behavior of the system is initially a stable equilibrium when a = 0. Incrementing a by 0.1, the long-term behavior changes when a = 7.2**

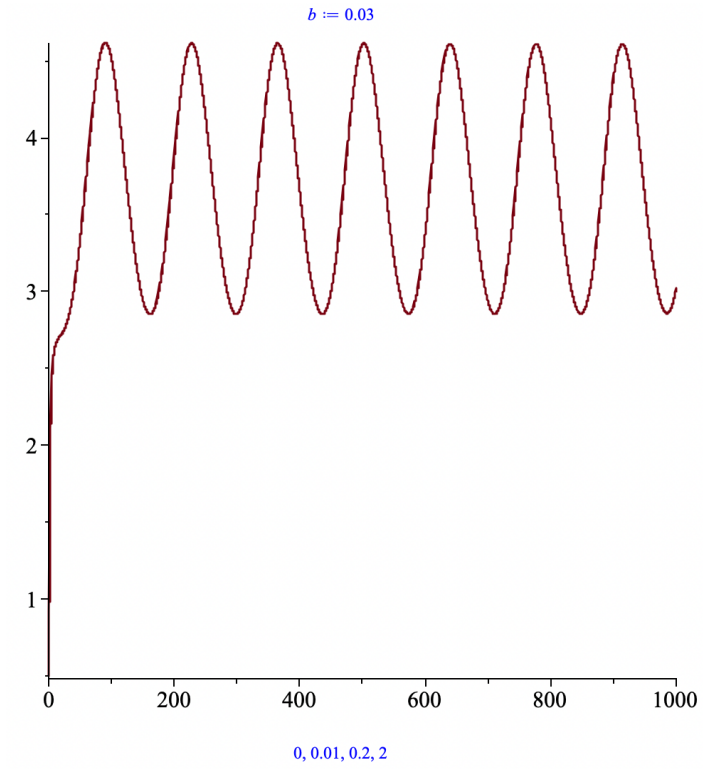
b = the ratio of the rate of decay of protein to mRNA



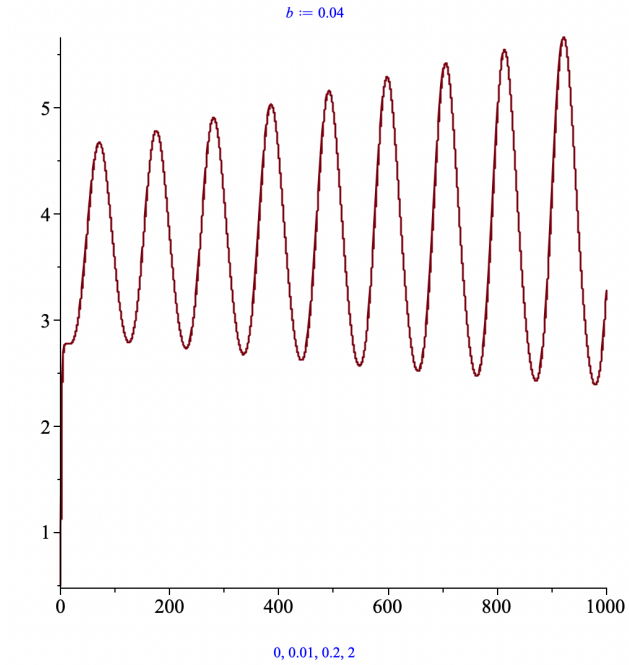
(a0,a,b,n) = (0, 50, 0, 2)



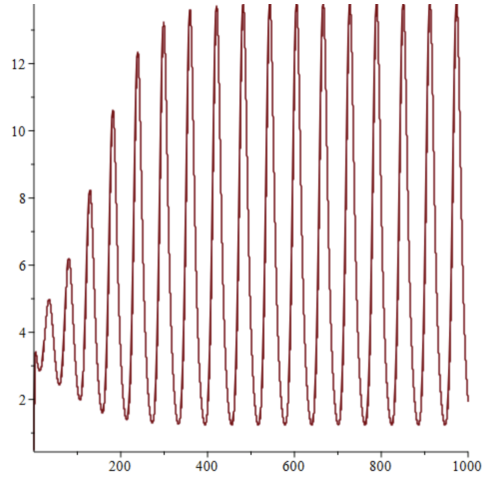
(a0,a,b,n) = (0, 50, 0.02, 2)



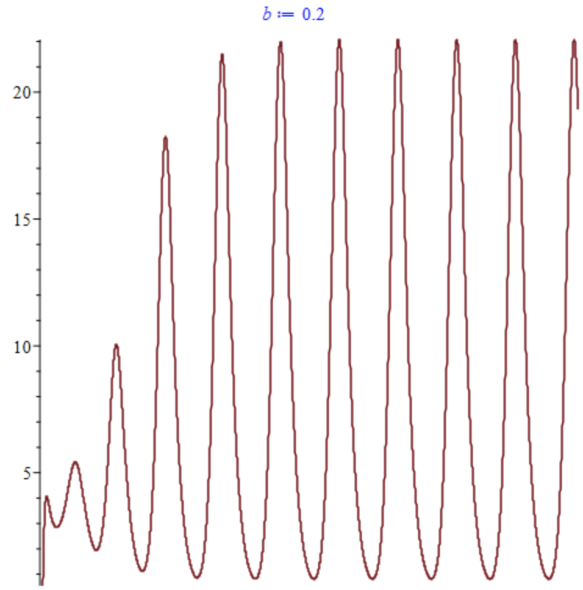
(a0,a,b,n) = (0, 50, 0.03, 2)



(a0,a,b,n) = (0, 50, 0.04, 2)



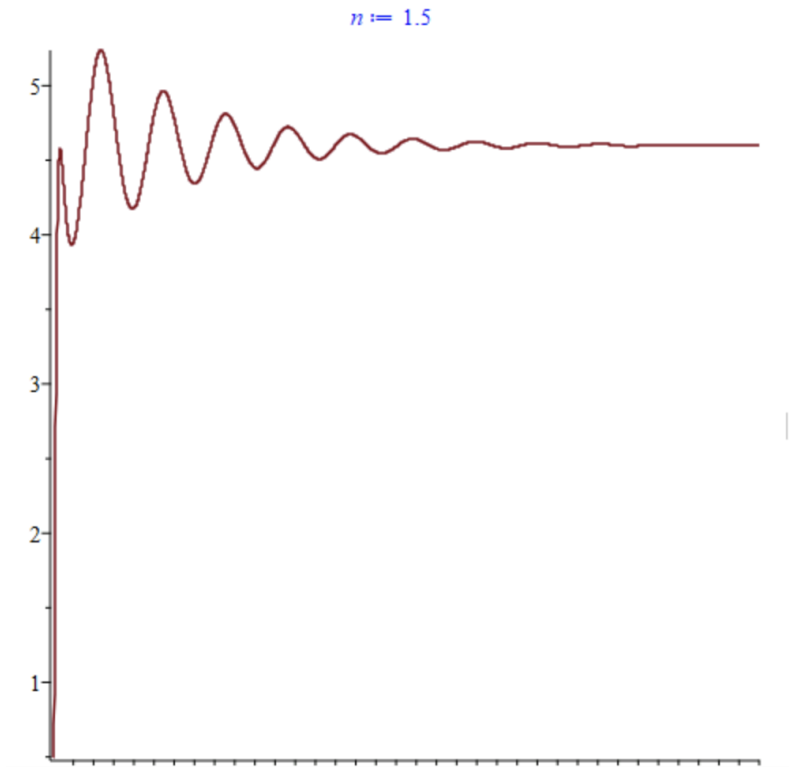
(a0,a,b,n) = (0, 50, 0.1, 2)



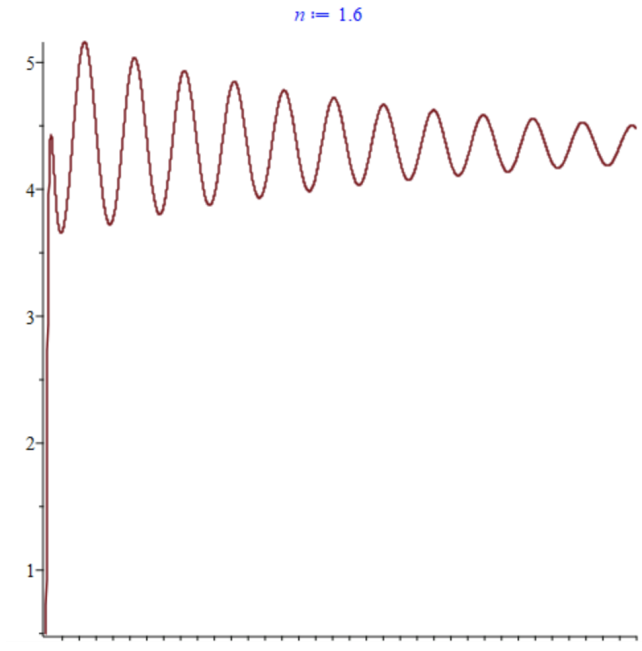
(a0,a,b,n) = (0, 50, 0.2, 2)

- The oscillations increase as b increases. When proteins and mRNAs have similar degradation rates, the mRNA degradation rate is the smallest. Therefore, a higher ratio of rate of decay would result in a decrease of the synthesis of mRNA.
- **The long-term behavior of the system is initially a stable equilibrium when b = 0. Incrementing a by 0.01, the long-term behavior changes when b = 0.03**

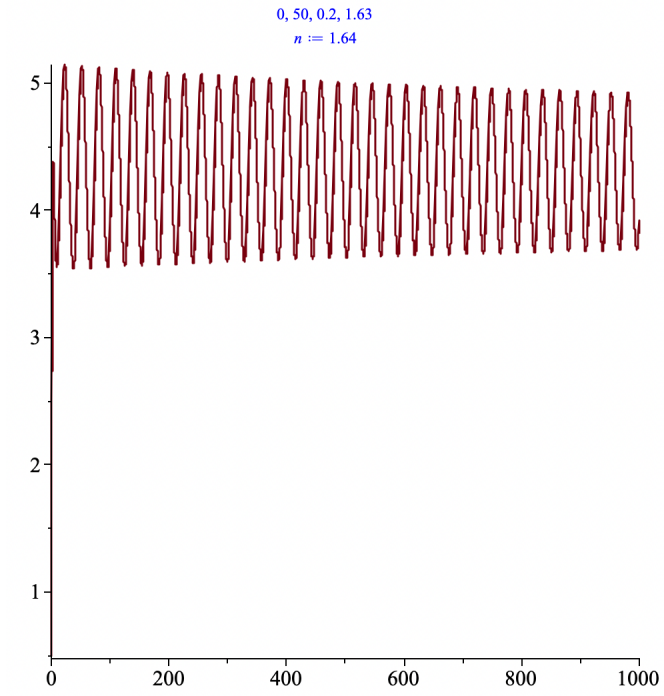
n = a “cooperativity” coefficient in the function describing the concentration dependence of repression



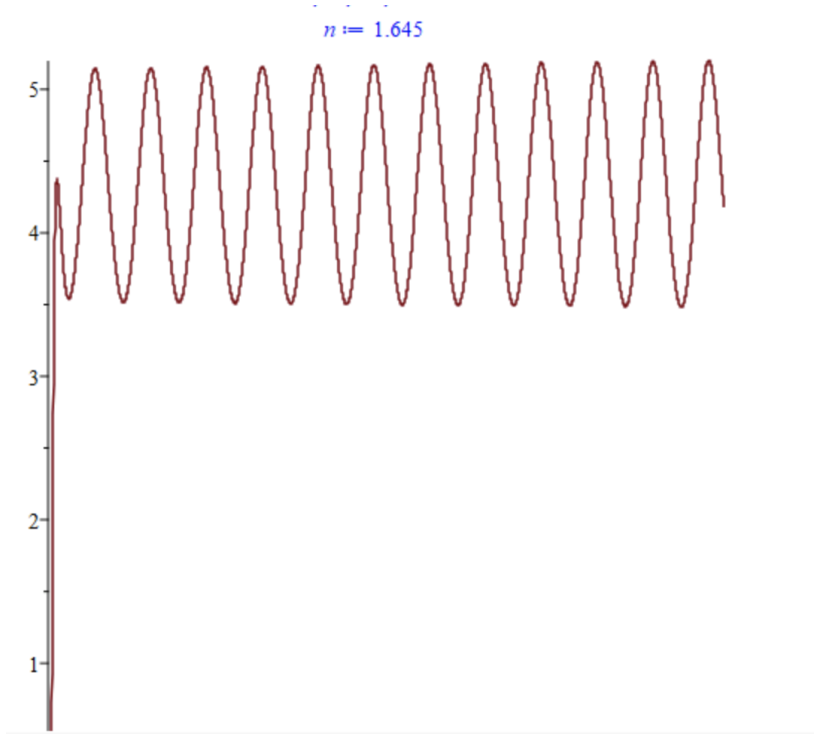
(a0,a,b,n) = (0, 50, 0.2, 1.5)



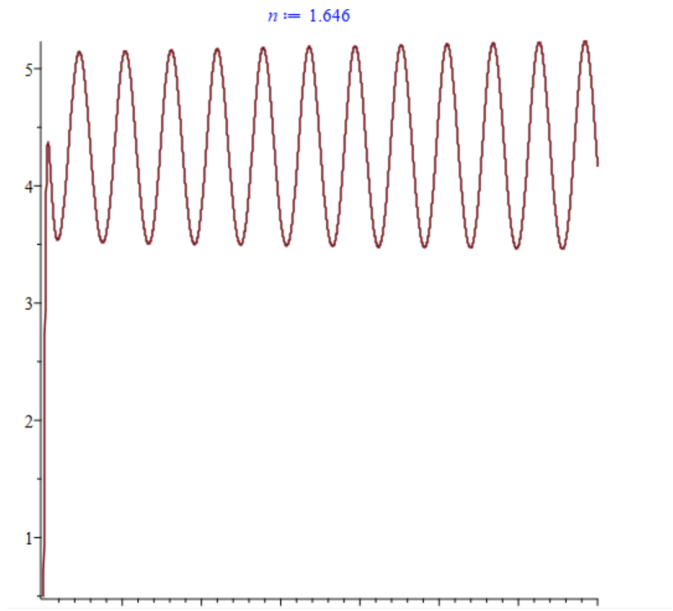
(a0,a,b,n) = (0, 50, 0.2, 1.6)



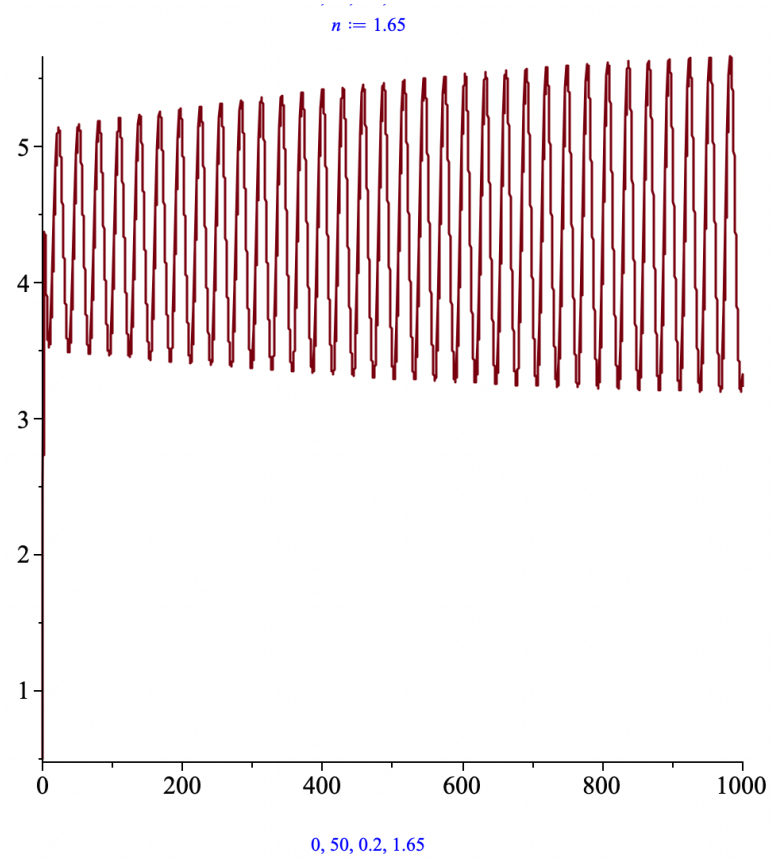
(a0,a,b,n) = (0, 50, 0.2, 1.64)



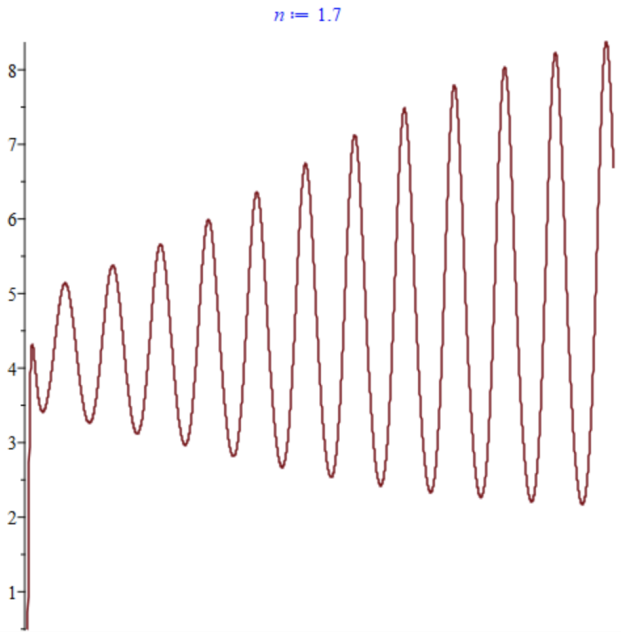
(a0,a,b,n) = (0, 50, 0.2, 1.645)



(a0,a,b,n) = (0, 50, 0.2, 1.646)



(a0,a,b,n) = (0, 50, 0.2, 1.65)



(a0,a,b,n) = (0, 50, 0.2, 1.7)

- N - Hill coefficient (how easily the repressor is able to bind to the promoter). A larger N value would indicate that the repressor is more easily able to bind to the promoter, therefore decreasing transcription rate. A larger N value would result in more oscillation in the network model.
- **The long-term behavior of the system is initially a stable equilibrium when n = 0. Incrementing a by 0.001, the long-term behavior changes when n = 1.646**